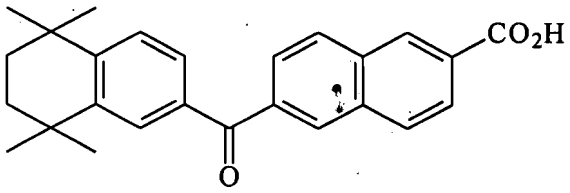
or benzophenone derivative:



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REMARKS

In accordance with the present invention, various compounds have been discovered that selectively interact with a single steroid or steroid-like receptor subtype to a much greater extent than with other steroid receptor subtypes. Such compounds are useful for the selective treatment of steroid responsive disease states because they minimize the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

By the present communication, claim 1 is amended, and new claims 16-18 are added, to define Applicants' invention with greater particularity, while claims 2-4 and 12-15 have been canceled to avoid subject matter that is covered in a related application, which resulted in the issuance to Applicants of U.S. Patent No. 5,668,115. New claims 16-18 replace canceled claims 9-11. No new matter is introduced by the subject amendments as all amended and new

claims fully supported by the specification and original claims. Claims 1, 5-8 and 16-18 are currently pending herein.

The abstract

The Office Action indicates that the application does not provide an abstract and, hence, fails to meet the requirement of 37 CFR 1.72(b). To meet the requirement of the statute, Applicant submits herewith an Abstract numbered as page 18 of the Specification. Entry of the Abstract is hereby requested.

The Rejection Under 35 U.S.C. § 112, First Paragraph

In traversal of the rejection of claims 1-15 for allegedly failing to provide an enabling disclosure, Applicant disagrees with the following assertion in the Office Action:

> . . . the specification does not disclose and [sic] effective dose interval for treating. . . . The concentration range of 106 to 109 is not a dose range because this range merely refers to an in vitro binding assay and not a therapeutic dose. Determining the effective dose to treat leukemia for each ligand would require undue experimentation. The specification defines significantly greater as a ligand which has a higher therapeutic index for treatment of the target disease. A therapeutic index estimates the safety of a drug and is the ratio of the toxic to therapeutic dose. Applicant does not provide the toxic dose range for the ligands.

(Office Action, pages 2-3). Applicants' specification clearly demonstrates the pharmacological activity of various ligands that selectively interact with a particular steroid receptor subfamily to a significantly greater extent than with other receptor subfamilies. Moreover, the cis/trans *in*

vitro assays employed to identify such ligands are clearly generally accepted by those of skill in the art as predictive of human activity for the type of ligand tested (see, e.g., U.S. Patent Nos. 5,071,773, and the like). Applicants submit that those of skill in the art could readily conduct similar tests of other receptor classes recited in the present claims using Applicants' teachings regarding steroid receptor subfamilies as guidelines.

In addition, although the specification does not provide Examples showing *in vivo* data, the lack of *in vivo* data is not fatal to enablement of the present claims. As recently stated by the Patent Office Board of Patent Appeals and Interferences:

> Case law. . . is receptive to early filing of applications in the biomedical field so long as the patent applicant. . . can provide evidence showing substantial activity in screening tests customarily used and accepted as predicative [sic] of human activity for the type of chemical tested.

Ex parte Aggarwal, 23 *USPQ2d* 1334, 1339 (1992). It is respectfully submitted that the *in vitro* data provided in Applicants' specification is precisely the type of evidence customarily used and accepted as predictive of human activity for the receptor subtypes tested.

Moreover, Applicants assert that the *in vitro* testing of the specification would enable one of skill in the art to determine through clinical trials what an effective dosage would be. Indeed, effective dosages are something that will ultimately be decided on the basis of clinical testing. The courts have acknowledged that the FDA process is more suitable for determining safe and effective dosages, and that such specificity is not required as a prerequisite

to obtaining a patent. See, e.g., *In re Krimmel*, 130 *USPQ* 215 (CCPA 1961); and *In re Hartop*, 135 *USPQ* 419 (CCPA 1962). As stated by the CCPA:

> [e]arly filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

In re Bundy, 209 *USPQ* 48 (CCPA 1981). Thus, it is respectfully submitted that Applicants' disclosure enables those of skill in the art to practice the claimed method without undue experimentation.

In general, the enablement requirement of 35 U.S.C. § 112, first paragraph, is considered to be satisfied if the specification teaches those of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 224 *USPQ* 409. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. Thus, for example, Applicants' specification discloses selective dose response curves for the interaction of various compounds with retinoid receptors (See Examples I-V). Based upon these guidelines, those of skill in the art can routinely determine effective dosage ranges for such compounds without any undue experimentation during the course of clinical trials. Therefore, it is the position of the Applicants that the skilled artisan has been provided with more than adequate information to practice the invention methods as claimed. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-15 for alleged indefiniteness is respectfully traversed. The rejection is moot as to claim 12, as it is canceled herein. Regarding claim 1, Applicants respectfully disagree with the Examiner's assertion:

> The claims are drawn to a method of treating a subject with a given condition. This is unclear as to what the subject [sic] is being treated in the subject. The claims merely define a group to whom the compounds are to be administered and do not recite a condition to be treated. Applicant also claims treatment with ligands which bind to specific receptor subtypes to a significantly greater extent than other subtypes. Since one would not know the extent to which a ligand would bind other subtypes when treating a patient for leukemia, one would not know if one was infringing the claimed invention.

(Office Action, page 3, lines 5-11).

Claim 1 is not drawn to the treatment of a subject in general, but requires that the subject being treated is "afflicted with a steroid or steroid-like hormone-responsive disease state". Thus, it is believed that original claim 1 is already in a form that avoids the type of indefiniteness alleged in the Office Action. However, in order to reduce the pending issues, claim 1 is amended herein to recite a method for treatment of a steroid or steroid-like hormone-responsive disease state "in a subject in need thereof". It is respectfully submitted that the amendment to claim 1 renders moot the rejection for lack of definiteness because those of skill in the art would understand that the subject to be treated is one having a steroid or steroid-like hormone

responsive disease associated with the selected receptor subtype. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Rejection under 35 U.S.C. § 103

The rejection of claims 1-15 under 35 U.S.C. § 103 over Crettaz et al. (1990), Biochem. J., 272:391-397; Astrom et al. (1990), BBRC, 173(1):339-245; EPA 0170105 ('105); and EPA 0220118 ('118), is respectfully traversed. Applicants' invention, as defined by claim 1, distinguishes over the references relied upon, taken alone or in combination, by requiring the administration of an effective amount of a ligand which selectively interacts with the steroid or steroid-like hormone responsive receptor subtype associated with the disease state being treated, to a significantly greater extent than with other subtypes of the same class.

It is respectfully submitted that Crettaz does not disclose or suggest any compounds which distinguish between subtypes of the same class of receptors (e.g., between subtypes RAR and RXR). The Examiner alleges that Crettaz teaches compound III as selectively binding specific RAR receptor subtypes.

> Crettaz teaches compound III selectively binds RAR receptor subtypes (page 395, Table 3, No. 6 and first column bridged to second column) and their use to treat retinoid responsive skin disorders and cancer (page 391, column 1, first paragraph). Astrom teaches compound II, etretin (page 340, "Materials") may be useful as an antitumor and antipsoriatic agent (page 339, first paragraph). '105 teaches retinoids for treating leukemia specifically on page 1 bridged to page 2 and compounds encompassing applicant's compound III for treating malignant

> diseases (abstract and pages 2-4). '118 teaches compounds encompassing applicant's compound IV for treating cancer and skin disease (see page 1). The method of treating subjects afflicted with steroid responsive diseases would have been obvious to a routineer because applicant's compounds were known to be useful for treating cancer and skin diseases.

(Office Action, page 4). However, Crettaz is silent as to the reactivity of any retinoid compounds with RXR. Thus, Crettaz does not teach a ligand which selectively interacts with a steroid or steroid like hormone-responsive receptor subtype associated with the disease state being treated, to a significantly greater extent than with other subtypes of the same class.

Likewise, Astrom does not disclose or suggest any compounds which distinguish between subtypes of the same class of receptors (e.g., RAR v. RXR receptors). Indeed, there is no recognition in the Astrom reference of any compounds having selectivity against RXR receptor.

It is respectfully submitted that EPA '105 is unable to cure the deficiencies of Crettaz and Astrom, as EPA '105 does not disclose or suggest the use of compounds which have the selective ability to react with members of one specific steroid or steroid-like hormone-responsive receptor subtype (e.g., RAR versus RXR), relative to other subtypes of the same class.

Further reliance on EPA '118 is unable to cure the deficiencies of Crettaz, Astrom, and EPA '105. Similar to the other three references relied on, EPA '118 does not disclose or suggest the use of compounds which have the selective ability to react with members

of one specific steroid or steroid like responsive receptor subtype (e.g., RAR versus RXR), relative to other retinoid responsive receptor subfamilies.

As neither Crettaz, Astrom, EPA '105, nor EPA '118 discloses or suggests the use of ligands that are selective for specific steroid or steroid-like hormone-responsive receptor subtypes, the combination of references relied upon does not disclose or suggest Applicants' claimed method. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on claims 1, 5-8 and 16-18 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 10/1/98

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Attachment: Abstract